

A Clearer View of TCE

Evidence Supports Autoimmune Link

More than 80 known or suspected autoimmune disorders—such as Crohn disease, multiple sclerosis, and rheumatoid arthritis—affect 5–8% of the U.S. population, according to the National Institute of Allergy and Infectious Diseases. The underlying causes of these disorders remain largely unknown, but one agent suspected to play a role is trichloroethylene (TCE), a solvent widely used in industrial and household applications. Researchers from the U.S. Environmental Protection Agency's National Center for Environmental Assessment and the Medical University of South Carolina searched the scientific literature for studies linking TCE with selected immunologic connections, including immunosuppression, hypersensitivity, and autoimmune-related effects [EHP 117:696–702; Cooper et al.]. On the basis of their review, the authors concluded that the evidence to date in mice and humans supports an etiologic role of TCE in autoimmune disorders.

Substantial evidence from mechanistic, clinical, and epidemiologic studies indicates that exposure to TCE and/or its metabolites (including chloral hydrate, trichloroacetic acid, trichloroacetaldehyde hydrate, and dichloroacetyl chloride) could influence the incidence

of autoimmune disorders. Research on autoimmune mouse models, including the MRL^{+/+} lupus mouse, has provided strong and consistent support for a role of TCE; this has included studies of exposures at environmentally relevant concentrations through multiple routes (inhalational, dermal, and oral). Studies of humans with high occupational or environmental exposures have also shown links between TCE and inflammatory immune responses, systemic sclerosis (scleroderma), and a severe generalized hypersensitivity skin disorder.

However, the authors also point out major gaps in our knowledge of TCE's effects on the immune system. In particular, data pertaining to measures of immunosuppression in humans are very limited, and potential effects of age or sex on susceptibility to autoimmune-related effects of TCE exposures, as well as effects of variation in exposure dose, timing, and duration, have yet to be established.

Because individual autoimmune diseases are relatively rare, it is difficult to assemble enough cases to conduct adequately powered epidemiologic research. However, the authors assert that the findings of recent experimental and observational studies of TCE provide a strong rationale for developing multisite collaborations to address the potential influence of TCE and other solvents on the incidence of autoimmune disorders. Such research would be facilitated by the establishment of state and national autoimmune disease registries. —Bob Weinhold

Bisphenol A, Chapter 2

New Data Shed Light on Exposure, Potential Bioaccumulation

Bisphenol A (BPA), an industrial chemical used in a variety of consumer products, is ubiquitous in the modern environment, with residues found in the urine of an estimated 93% of Americans over 6 years of age, according to data from the 2003–2004 National Health and Nutrition Examination Survey (NHANES). Recent research indicates that BPA acts as an endocrine disruptor and may increase the risk of heart disease, diabetes, and liver problems in adults. Until now, most exposure was thought to occur through diet, and the chemical was thought to clear the body quickly and completely. But a new study shows that urine BPA levels of subjects who had fasted for several hours were not as low as expected, suggesting either nondietary exposures or accumulation in fatty tissue, or both [EHP 117:784–789; Stahlhut et al.].

Although BPA is fat-soluble and thus can accumulate in fatty tissues, animal and human data suggest it tends to be rapidly metabolized, with elimination thought to be virtually complete within 24 hours of acute exposure. To gain a better understanding of how BPA clears the body, investigators in the current study used data from 1,469 adult participants in the 2003–2004 NHANES. Study participants (excluding children and insulin-dependent diabetics) had

been asked to fast for at least 6–9 hours. Using the urine drawn from each study participant, the investigators modeled log BPA concentration against fasting time, adjusting for urine creatinine and other confounders, to estimate what they called the “population-based half-life” of BPA for a 0- to 24-hour fasting period.

Previous studies have reported that BPA has a urinary elimination half-life of only 4–5 hours, but BPA levels in this population declined much more slowly, showing a drop from adjusted population peak to trough levels of only 46% by 17 hours. Although there was a relatively rapid decline in BPA levels during the 4.5- to 8.5-hour fasting interval, the BPA slope was essentially flat between 8.5 and 24 hours, suggesting very slow or minimal elimination during that time.

The findings are consistent with two possible explanations—first, that BPA exposure occurs through means other than food, and second, that BPA accumulates in body fat, from which it is gradually released over time. The authors conclude that their findings highlight the need for additional research on chronic BPA exposure, identification of significant nonfood sources of exposure (which may include dental composites and sealants, household dusts, air, recycled and carbonless paper, and the PVC pipe approved for use in residential water supply lines in many cities), and confirmation of reported data on bioaccumulation of the xenoestrogen in human adipose tissue. Confirmation of the current findings could lead to a reevaluation of BPA exposures in risk assessment studies. —Tanya Tillett



New findings raise the possibility that nonfood BPA exposure may be more substantive than previously thought.

Clockwise from top left: Danil Vachegim/Stockphoto; Serhiy Zavalnyuk/Stockphoto; Corbis; Danish Khan/Stockphoto

The Yin and Yang of Exposure

Chemical Combinations May Explain Feminization of Wild Fish

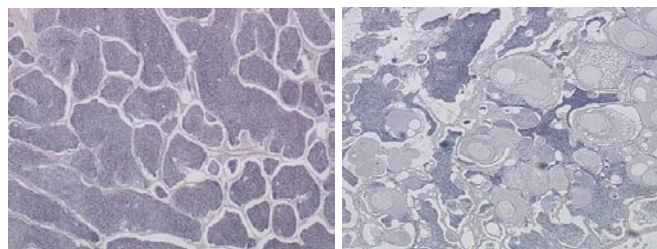
More than 100,000 substances occur in wastewater effluent, including an array of endocrine disruptors such as human and veterinary pharmaceuticals, natural and synthetic hormones, detergents, and industrial chemicals. Studies have linked estrogenic wastewater pollution with feminization of males in downstream fish populations. However, findings from rodent models of testicular dysgenesis syndrome, a spectrum of environmentally linked male reproductive disorders in humans, indicate that both estrogens and antiandrogens may be contributing to health effects in tandem. A new study that models exposure to both estrogenic and antiandrogenic compounds in wild fish now suggests that combinations of these compounds, rather than estrogenic compounds alone, may be responsible for the endocrine disruption observed in these animals as well [*EHP* 117:797–802; Jobling et al.].

To help elucidate the complex relationships and interactions among the various types of endocrine disruptors (estrogenic, anti-estrogenic, androgenic, and antiandrogenic), the authors created statistical models based on 1) the chemicals' known hormonal activities in recombinant yeast screen assays and 2) concentrations measured during an earlier national survey in effluent from U.K. wastewater treatment plants. The models also included hydrologic data to enable estimation of river-water chemical concentrations at specific sites and national survey data on the location and prevalence of feminized male fish. The statistical models first accounted for estrogenic effects observed in fish, then included effects associated with antiandrogens and other compounds.

The authors previously found a very strong correlation between the predicted steroid estrogen content of U.K. rivers and feminization in male wild fish. In the current study they focused on four specific traits of feminization: elevated plasma levels of vitellogenin (an egg

yolk precursor protein normally produced only in females), feminized reproductive ducts, oocyte (egg cell) development in the testes, and the number of oocytes found in the testes. Once the main factors accounting for variation were identified, the researchers were able to distinguish the respective contributions of estrogens and antiandrogens to biologic responses and explore potential interactions.

Model estimates suggested that male fish exposed to the highest concentrations of estrogens or antiandrogens were the most likely to be feminized. However, chemical combinations were also important. Estrogens and antiandrogens acted additively with regard to oocytes in the testes, but estrogens appeared to antagonize effects of antiandrogens on feminization of the reproductive duct. The authors



The micrograph on the left shows normal testis tissue from an adult male roach (*Rutilus rutilus*). On the right is the testis of a severely feminized male roach; the large circular inclusions are oocytes.

note that combined effects were not necessarily due to simultaneous exposure; for example, one compound could serve as an initiator early in life while another could act as a promoter later in life. On the basis of these analyses, the authors suggest that sexual disruption in male wild fish populations may be related to exposure to a combination of both estrogenic and antiandrogenic compounds, a relationship that may also hold true for humans. —Julia R. Barrett

Nutrient Protection against Arsenic Toxicity

Folate, Cysteine Support Methylation in Children

Nutritional factors are known to influence arsenic metabolism in adults, and poor nutritional status—as reflected in part by a lack of various B vitamins and antioxidants—is thought to confer greater susceptibility to arsenic toxicity. Now researchers working in Bangladesh have reported that deficits in the B vitamin folate and the amino acid cysteine may adversely influence arsenic metabolism in children [*EHP* 117:825–831; Hall et al.]. The research team also found that, compared with adults, children may metabolize arsenic more efficiently and excrete it more readily, regardless of folate status.

Chronic exposure to arsenic, a known human carcinogen, occurs mainly through contaminated drinking water and currently affects about 140 million people worldwide, including 35 million Bangladeshis. Such exposure has been linked to increased risks of cardiovascular disease and cancers of the skin, bladder, lung, and liver. Childhood exposure also increases the risk of intellectual deficits and respiratory disorders, among other health problems.

Arsenic metabolism involves two methylation steps that rely on folate: Inorganic arsenic (InAs) is first converted to monomethylarsonic acid (MMA), which is then converted to the less toxic dimethylarsinic acid (DMA); this process facilitates urinary arsenic elimination. In the current study, the team measured urinary levels of InAs, MMA, and DMA, as well as blood levels of the metabolic by-product homocysteine

and an array of micronutrients (including folate, cysteine, and cobalamin) in 165 6-year-old children. Among the participants, 4.1% of females and 3.3% of males were classified as folate deficient.

Consistent with previous research findings involving adults, higher levels of folate and cysteine correlated with a lower proportion of unmethylated arsenic metabolites in the urine, indicating that adequate levels of these nutrients may be important for arsenic methylation in children. In addition, compared with Bangladeshi adults, children had lower mean proportions of urinary InAs and MMA as well as higher mean proportions of urinary DMA.

The study did turn up a surprise: Plasma homocysteine was inversely correlated with the proportion of MMA in urine, especially in males, but was positively correlated with DMA in urine. Compared with previous findings for adults, the children were also more likely to have high homocysteine levels, despite being less likely to be classified as folate deficient. More research is required to confirm this finding and the underlying mechanisms.

The authors hypothesize that the one-carbon metabolism mechanism behind methylation may be upregulated during periods of rapid growth to meet high demands for DNA and protein biosynthesis. This upregulation would also be associated with an increase in homocysteine biosynthesis. At the same time, behaviors common among Bangladeshi adults—such as cigarette smoking and the chewing of betel nuts—could also play a role in altering arsenic methylation patterns. Overall, this study's findings indicate that improved nutritional status could constitute a key strategy for reducing the risk of arsenic-related disease in Bangladeshi children. —Kris Freeman